CAP REPORT

NUMBER 10

Drugs and the Third World: Phenacetin Risks, Benefits and Marketing in Malaysia

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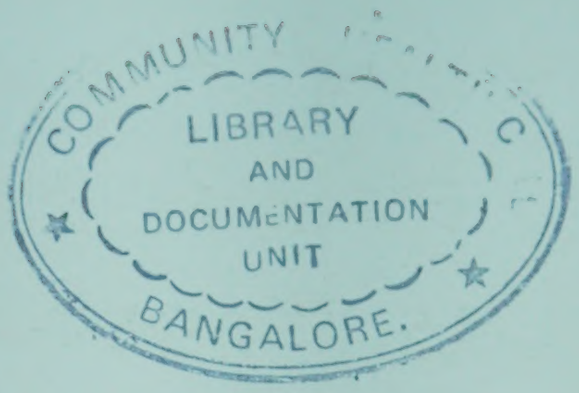

Drugs and the Third World:

Phenacetin Risks, Benefits and Marketing in Malaysia

COMMUNITY HEALTH CELL
326 V Main, I Block Koramangala
Bangalore – 560 034

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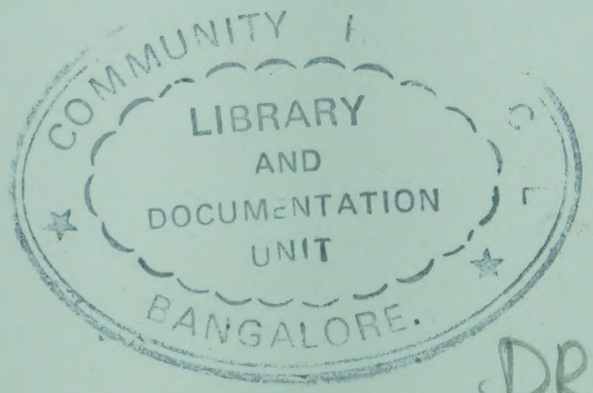
Published by

Consumers' Association of Penang
87 Cantonment Road,
Penang, Malaysia.

The Consumers' Association of Penang is a voluntary non-profit organisation which fights for the rights and interests of all consumers through research, educational and representational activities.



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Printed by

Jutaprint
54, Kajang Road
Penang, Malaysia.

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ISBN 967-9950-25-5

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PREFACE

Many harmful pharmaceutical drugs which are banned or severely restricted in many countries are still being marketed and used in developing countries like Malaysia. One such drug is phenacetin.

In this report, the adverse effects and dangers of this drug are examined. Phenacetin in combination with aspirin produces severe renal damage. In most cases phenacetin has been found to be sold to the public in the form of combination products. Prolonged daily use of these combination products containing phenacetin can cause severe kidney damage and should not be allowed.

In the *Medical Journal of Malaysia* (Vol 38 No 4 Dec 1983) it was reported that out of 1118 people questioned in a survey, 0.5 - 2.0% had consumed enough analgesic to meet the criteria of analgesic abuse. In that survey, the reason most often quoted for consuming analgesics was headache and the commonest analgesic consumed was paracetamol, followed by Chap Kaki Tiga and Chap Harimau. Chap Kaki Tiga is a local preparation which used to contain aspirin, caffeine and phenacetin. The phenacetin has since been replaced with acetaminophen (Ibid: 284).

Another example worth quoting is that of a survey done by a doctor in Sarawak in October 1980 where he found that the natives suffered gastric bleeding. This was the result of excessive consumption of the analgesic, Chap Kaki Tiga for minor ailments like bodyache and fever.

Following reports of the toxic effects of phenacetin, many countries have either banned its use in analgesic preparations or severely restricted its use. These countries include Canada, the United States, the United Kingdom, New Zealand, Romania, Saudi Arabia, Sweden, Turkey, Yemen, Denmark, Suriname, Israel and Cyprus. In Malaysia, although phenacetin is listed as a Group B Poison, it is still being sold to the public in combination with other drugs. The availability of such products may lead to excessive consumption of phenacetin.

This report hopes to alert the Ministry of Health to the dangers and toxicity of this analgesic drug and to call for a ban on its use in this country, so as to ensure the safety and health of Malaysian consumers.

S M Mohd Idris, JP
President
Consumers' Association of Penang
1986

Update

This report was presented to the Ministry of Health, Malaysia, in July 1986. On 5 October 1986, the Director of Health, Tan Sri Abdul Khalid, announced that phenacetin, together with six other drugs, has been banned in Malaysia. Manufacturers and distributors would be given three months' grace to withdraw all products containing phenacetin from the market.

CHAPTER 1

INTRODUCTION

Phenacetin is an antipyretic as well as a mild analgesic commonly used in combination with other drugs. Analgesics, including compound analgesics, are widely available in Malaysia and can be obtained without prescription. Many of them can be purchased from local provision stores as well as Chinese medicine shops.

Until quite recently, there were many brands of compound analgesics on the market containing aspirin, phenacetin and caffeine. Two local brands of such compound analgesics are Chap Kaki Tiga and Chap Harimau. Since 1981, phenacetin has been replaced by acetaminophen in Chap Kaki Tiga and salicylamide in Chap Harimau (Segasothy 1983: 284). However, it has been found that the original preparations containing aspirin, phenacetin and caffeine are still available in some parts of the country, especially in rural areas.

It was reported that Chap Kaki Tiga and Chap Harimau were among the most commonly consumed analgesics (Segasothy, et al, 1984: 23). The combination of aspirin and phenacetin produces a more severe renal damage than either drug alone. It was initially believed that it is phenacetin which is

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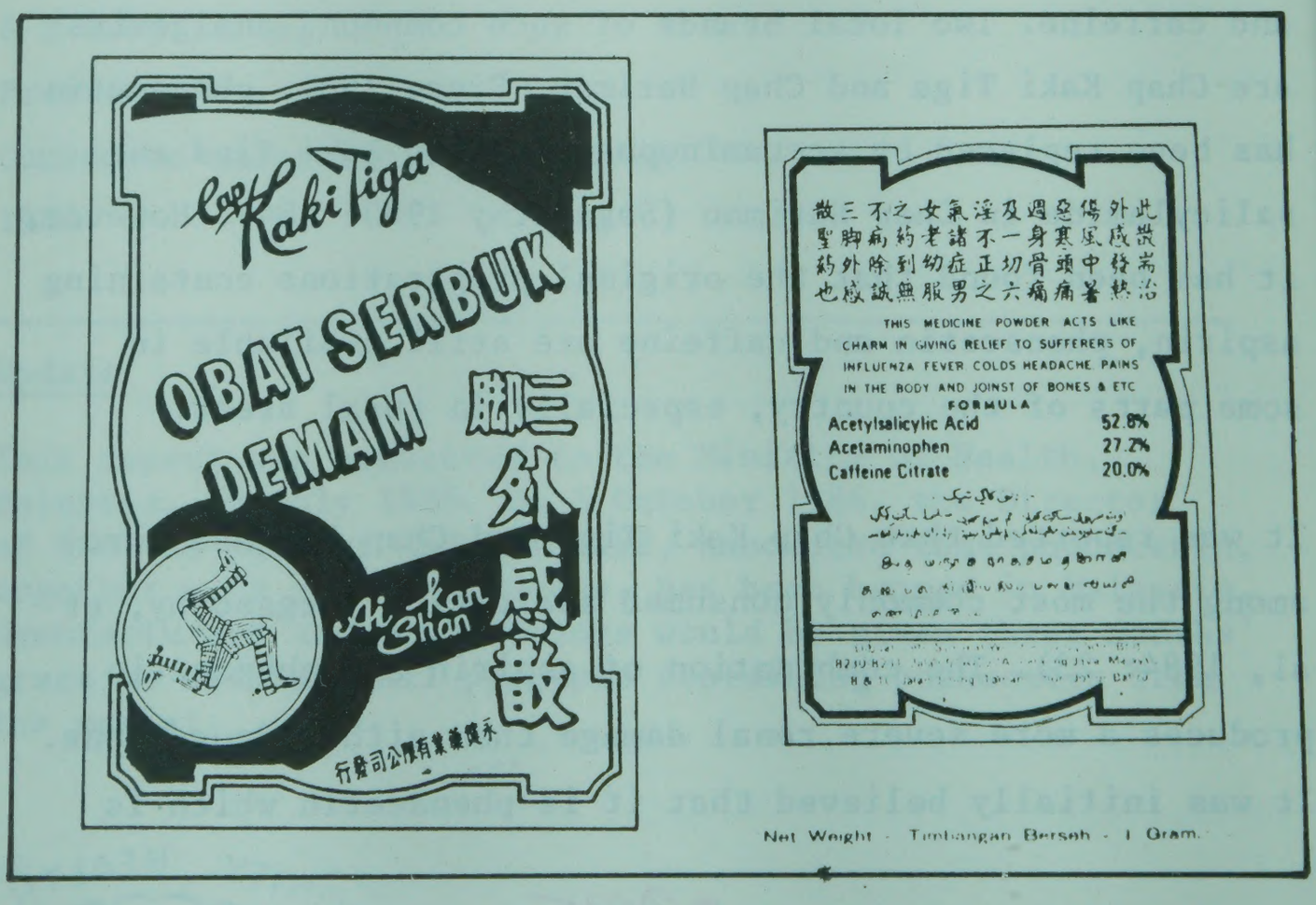
Top: the old Chap Kaki Tiga which contained phenacetin, and bottom: the new formula in which phenacetin has been removed. Nevertheless, the old preparation can still be obtained in some parts of Malaysia.



the major cause of renal damage, but experimental studies in rats by Nanra et al have shown that aspirin has a more deleterious effect than phenacetin and the combination of both potentiates the nephrotoxic effect.

In the United Kingdom and in most states in Australia, the sale of compound analgesic drugs has been restricted to those with prescription. And phenacetin has been either severely restricted or banned in more than 10 countries worldwide.

In Malaysia, however, compound analgesics are easily available and phenacetin continues to be used. Although phenacetin is listed as a Group B Poison, meaning that according to the law, it can be dispensed only by a medical practitioner on prescription, combination products containing the drug are freely sold to the public.

This report by the Consumers' Association of Penang urges the Ministry of Health to immediately review the benefit of phenacetin, bearing in mind the toxicity of the drug and its harmful effects. In the light of all the facts presented, only a total ban on phenacetin can protect consumers from the dangers of the drug.

CHAPTER 2

PHENACETIN: INN (International Nonproprietary Name Selected by WHO)

Other Generic Names: Acetophenetidin, Paracetophenetidin

Phenacetin was first introduced in 1887 (Laurence 1973: 12.2). It is an effective mild analgesic which is commonly used in combination with others (Ibid: 12.28). It is an antipyretic (reduces fevers) but has no anti-inflammatory or useful antirheumatic effect effect (Ibid). Phenacetin is broken down in the body to paracetamol which is widely used as a mild pain reliever (Parish 1976: 406).

Phenacetin is generally considered as approximately equipotent with paracetamol and aspirin as an antipyretic. Its antipyretic action is probably via a direct effect on the hypothalamic heat-regulating centre (that part of the brain which regulates heat) to augment the dissipation of body heat (*Berita Farmasi* Vol 6 No 2, 1979).

According to *The Clinical Toxicology of Commercial Products* (4th ed 1976), phenacetin has a toxicity rating of 4 on the Toxicity Rating Chart, on a scale of 1 (lowest) to 6 (highest). This means that the drug is very toxic.

Phenacetin is suspected of having an addiction liability. A case has been reported of a housewife who, over a period of five years, ingested 77 lb of phenacetin before succumbing to a fatal nephritis (Ibid).

During a flu epidemic in a Swedish town in 1918, a doctor prescribed a powder containing phenacetin, phenazone and caffeine. Many people died from the epidemic, but those who survived continued to take the powder because 'they felt fitter'. Powder taking became a habit like cigarette smoking. Deaths from renal insufficiency rose in the town but the powder takers who had become emotionally dependent on their powders resisted enquiries and refused to cooperate with investigations (Laurence 1973: 12.29).

It was not until 1953 that phenacetin was suspected of causing kidney damage (Ibid). In 1961 phenacetin was withdrawn from sale to the public in Sweden and became a prescription drug (Ibid: 12.80).

(1) Actions

Phenacetin is an important ingredient of many analgesic mixtures used for somatic pain, usually in combination with aspirin, caffeine or codeine (Laurence 1973: 12.28).

Because of the link between kidney damage and the use of phenacetin, it has been suggested that phenacetin alone or in combination should never be used (Parish 1976: 407).

According to the British Committee on the Review of Medicines, 'Phenacetin has no place in analgesic, anti-pyretic and anti inflammatory therapy' (*Consumer Currents*, 16 May 1979).

Phenacetin is being replaced by paracetamol (which is the breakdown product of phenacetin) although the safety of paracetamol remains uncertain (Laurence 1973: 12.28) as evidence has shown that an overdose can cause liver and kidney damage and even death (*Berita Farmasi* 1974 Vol 1: 23 and Parish 1976: 183).

(2) Adverse Drug Reactions

Phenacetin appears to be associated with development of transitional-cell carcinoma of the renal pelvis (Margetts, 1974: 55). Phenacetin can cause sweating and sometimes skin rashes and jaundice (*Martindale* 28th ed: 205). In severe toxicity, convulsions and coma (Ibid) and circulatory collapse (Parish 1976: 183) may occur.

Prolonged use of large doses of phenacetin has been associated with renal papillary necrosis (kidney damage) (*Martindale* 28th ed) as well as liver damage (Parish 1976: 406). Phenacetin abusers have been suspected of having a high incidence of renal pelvic tumours (Laurence 1973: 12.30. Diabetics should not be given the drug (Ibid).

It has also been reported that phenacetin has an adverse effect on blood in that it can cause sideroblastic anaemia

(Girdwood 1976: 11, 394). When phenacetin has been taken in doses of 1 gramme or more daily, other blood disorders (methaemoglobinaemia and sulphaemoglobinaemia) have occurred where patients have gone blue as a result of an alteration in the pigment which carries oxygen in red blood cells. Occasionally, haemolytic anaemia has ensued (*Martindale* 28th ed: 205 and Parish 1976: 406).

Haemolytic anaemia has developed in G6PD*-deficient patients following the use of phenacetin (Silverman, et al, 1976: 268). Four cases of toxic epidermal necrolysis have been reported associated with the use of phenacetin or acetanilide (Lowney, et al, 1967: 95, 359).

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* This is a naturally occurring enzyme called glucose-6-phosphate dehydrogenase. G6PD deficiency is inherited in a sex-linked manner; males with this gene are affected whereas females with this gene are carriers. According to Professor Wong Hock Boon of the Singapore University, about 3% of all Chinese and Malay males and 6% of all Malay females possess this gene (Wong 1972: 131), and it is estimated that about 90,000 people in Singapore have this genetic disorder. Professor Wong revealed in a study in 1961 that 78% of the 32 cases of children in Singapore with haemoglobinuria were due to drug-induced haemolysis in patients with G6PD deficiency. The drugs implicated were sulphonamides, phenacetin and Vitamin K (Wong 1961, 2: 74).

(3) Studies on Phenacetin

As no epidemiological data on analgesic abuse was available in any Asian country, a survey involving selected groups in Malaysia was performed (Segasothy 1983). Three different groups of the population were chosen: 500 inpatients in the medical wards of the General Hospital, Kuala Lumpur, 431 residents of Kampung Pandan and 187 residents of two rubber estates. From the survey it was found that 0.5 - 2.0% of the people had consumed more than 2 kg of analgesics, an amount sufficient to meet the criteria of analgesic abuse. This amount is also sufficient to cause severe renal impairment. Between 4.6 and 9.6% of the people surveyed had consumed more than 250 g of analgesics. Whilst this is far below the amount required to cause renal damage, it is important to note that these subjects had been and were still taking analgesics regularly, and given sufficient time would eventually meet the criteria for analgesic abuse. The commonest analgesic consumed was paracetamol followed by Chap Kaki Tiga and Chap Harimau. The commonest reason for consuming analgesic was headache (Ibid).

In another survey done by a doctor in Sarawak in October 1980, it was found that many natives suffered from gastric bleeding as a result of excessive consumption of the analgesic, Chap Kaki Tiga. This analgesic was being used for minor ailments like bodyache and fever. In fact, even now it is common practice among them to start the day with Chap Kaki Tiga. Many have unknowingly become addicted to

the drugs, taking them daily.

In Sweden about three million phenacetin prescriptions used to be signed each year. When phenacetin was restricted, there was a reduction in the incidence of kidney disorders (Coleman 1977: 149).

Phenacetin was also found in many analgesic preparations in the United Kingdom. In March 1974, about 30 painkillers containing phenacetin were on sale in supermarkets (Ibid).

'It has been estimated that at least four hundred and fifty new cases of papillary necrosis caused by phenacetin occur in England and Wales each year leading to seventy-five deaths. It has also been estimated that 10 per cent of all cases of renal failure were caused by analgesics' (Ibid).

Studies in Britain over the last few years have shown that a daily dose of 1 gramme or more, or the equivalent of seven APC (aspirin-phenacetin-caffeine) tablets can cause rupture of the blood cells (*Consumer Currents* 16/5/79).

Because of its toxic effects, phenacetin has now been withdrawn from all proprietary analgesic preparations in the UK.

Phenacetin is not available as a single entity in the US but is found as a constituent of many prescriptions and over-the-counter (OTC) preparations. One of the best known

is aspirin-phenacetin-caffeine (APC). Phenacetin has not been permitted on the market as a single entity because it has been associated with nephrotoxicity when used chronically. In therapeutic doses (650 mg or less) it is probably as safe as acetaminophen. In overdoses, hepatotoxicity, nephrotoxicity and methaemoglobinaemia are potentially serious complications (but overdose is highly unlikely at the dosages used in the various proprietary compounds) (Neidle 1980: 340).

It was reported in the *Star* (2/8/85) that in Boston, USA, it had been found that the common painkiller phenacetin might cause bladder cancer in heavy users. This finding was the result of a study by researchers at the US FDA. In this newspaper report it was stated that phenacetin was commonly mixed with other ingredients and sold under a variety of prescription and non-prescription brand names including Fiorinal, Empirin and Soma Compound. The report further stated that a *New England Journal of Medicine* report had found that women who suffered from bladder cancer were six times more likely to be regular heavy users of phenacetin products than other women.

A study was done on rats by a group of researchers in Australia. It was found that renal papillary necrosis had been induced in 36.4 - 75% of rats which were gavage-fed (force-fed) with analgesic mixtures containing proprietary combinations of aspirin, paracetamol, phenacetin, phenazone, salicylamide and caffeine. These findings supported the

recommendations of the National Health and Medical Research Council that the availability of analgesic mixtures be restricted. In Australia, analgesic nephropathy continues to be responsible for 20% of cases of terminal renal failure which require treatment with dialysis and transplantation (Nanra, et al, 1980: 486-487).

Together with paracetamol, phenacetin is listed in the *Monthly Index of Medical Specialities (MIMS)*, Australia (Oct-Nov 1979, Vol 16 No 6: 36). It is contraindicated in 'Analgesic nephropathy' and Special Precautions state that 'chronic use should be avoided. Daily use of paracetamol may potentiate oral anticoagulants'. Under 'Toxic Effects' is stated: 'At high or prolonged dosage Phenacetin has caused methaemaglobinaemia, sulphaemaglobinaemia and haemolytic anaemia. Habitual use may also be associated with analgesic nephropathy. In acute overdosage both drugs may cause potentially fatal liver failure. This may take at least three days to develop with the major manifestation being jaundice, hypoglycaemia and metabolic acidosis.'

CHAPTER 3

REGULATIONS ON PHENACETIN WORLDWIDE

A number of countries have taken action to heavily restrict or ban the drug:

Canada

All preparations containing phenacetin in combination with any salt or derivatives of salicylic acid have been withdrawn from sale in Canada as from 1 July 1978 (*WHO DIB* July-Sept 1978: 20).

United States

In the US, a compulsory warning is required for any drug containing phenacetin which reads 'Phenacetin may damage the kidneys when used in large amounts or for long periods of time (*Physicians' Desk Reference* 1979: 926, 1804). The FDA has also rejected the use of phenacetin in home remedies because it was unsafe for this purpose (*WHO DIB* July-Sept 1977: 3).

United Kingdom

All products containing phenacetin were withdrawn from the

UK as from March 1980 because of the 'well-documented association between the long term use of phenacetin and nephropathy'. Certain exemptions will be allowed in relation to:

- the use of phenacetin as a stabiliser, in a maximum concentration of 1% w/w, (weight/volume) in solutions of hydrogen peroxide intended for external use.

- prescriptions filled by doctors for specific patients (combination products are excluded).

- drugs for export (*WHO DIB*, Oct-Dec 1979: 17).

New Zealand

This compound has been made prescription poison in New Zealand (*Consolidated List* 1983).

Romania

In 1982, the Minister of Health had recommended the gradual reduction in the use of phenacetin. It has now been phased out of use completely (Ibid).

Saudi Arabia

Phenacetin is not approved for use in Saudi Arabia because of the risk of liver damage as well as nephropathy (Ibid).

Sweden

As of January 1982, phenacetin has been banned for use and/or sale for domestic purpose owing to the risk of carcinogenicity and renal damage on long-term use and the presence of alternative therapy. Although Sweden has no legal powers to prohibit export, no export of this product occurs (Ibid).

Turkey

As of 1982, preparations containing phenacetin in combination with analgesics and antipyretics have been withdrawn by the Ministry of Health with the recommendation that such formulations be changed, owing to the risk of nephropathy from long-term use. Export of this product is prohibited by Turkey (Ibid).

Yemen

From 1979, preparations containing phenacetin have been withdrawn from use in Yemen (Ibid).

Denmark

The National Board of Health of Denmark has decided to withdraw the registration of pharmaceutical products containing phenacetin. This is in line with decisions taken in recent years in several other countries including Canada, Norway, Sweden, Ireland, the United Kingdom and

the USA (*WHO DIB*, Oct-Dec 1984: 23).

Suriname

The Ministry of Health of Suriname has also recently informed WHO of its decision to withdraw registration of all pharmaceutical products containing phenacetin (Ibid: 24).

Israel

The sale of analgesic combination products containing phenacetin has been prohibited in Israel from the end of 1980. Paracetamol has been recommended as a substitute for phenacetin (*WHO DIB* July-Sept 1980: 19).

Cyprus

Cyprus has adopted a similar position as Israel. Here all products containing phenacetin intended for internal use have been withdrawn as from July 1980 (Ibid).

Malaysia

Under the Poisons Ordinance 1952 and the Poisons List 1983, phenacetin is listed as a Group B Poison. This means that this drug can only be dispensed by a registered medical practitioner on prescription. However, combination products containing the drug are available on the market.

CHAPTER 4

DRUG INFORMATION AND BRANDS SOLD IN MALAYSIA

In Malaysia, doctors obtain information on phenacetin from three major sources. They are:

(a) *The Drug Index for Malaysia and Singapore (DIMS).* *DIMS* is a quarterly publication on ethical medicines available in Malaysia and Singapore. It is prepared by the pharmaceutical companies and distributed free to doctors in both countries.

(b) Drug advertisements and brochures which are distributed free to doctors by the drug companies.

(c) Drug inserts which come together with the drugs when they are purchased. The insert gives information on the use of the drug, the dangers and the precautions to be taken. The instructions and information on the drug insert are provided by the company which markets its particular brand product.

(1) Phenacetin Preparations Listed in DIMS

DIMS Vol 15 No 2 June 1986 lists 3 phenacetin preparations.

These are:

- Benza Forte Tablets (Takeda)
- Quadronal (Asta-Werke)
- Soma Compound (Carter Wallace)

Both Benza Forte and Soma Compound are Schedule B poisons which can be purchased only with a doctor's prescription. Quadronal in Malaysia, however, is listed in *DIMS* as a non-poison. In early 1986, CAP staff managed to purchase this preparation over the counter without an entry in the pharmacist's prescription book.

The manufacturers of the various phenacetin preparations, together with their contents, are listed in Table 1. From the Table it can be seen that the manufacturers of the drugs are all foreign.

TABLE 1: Phenacetin Preparations Available in Malaysia

Source: *DIMS* June 1986

	BRAND NAME	MANUFACTURER	CONTENTS	
1.	BENZA FORTE	Takeda (Japan)	Tripelennamine HCL	25 mg
			Metamizol	40 mg
			Phenacetin	50 mg
			Ethoxybenzamide	150 mg
			Caffeine	50 mg
			Ephedrine HCL	5 mg

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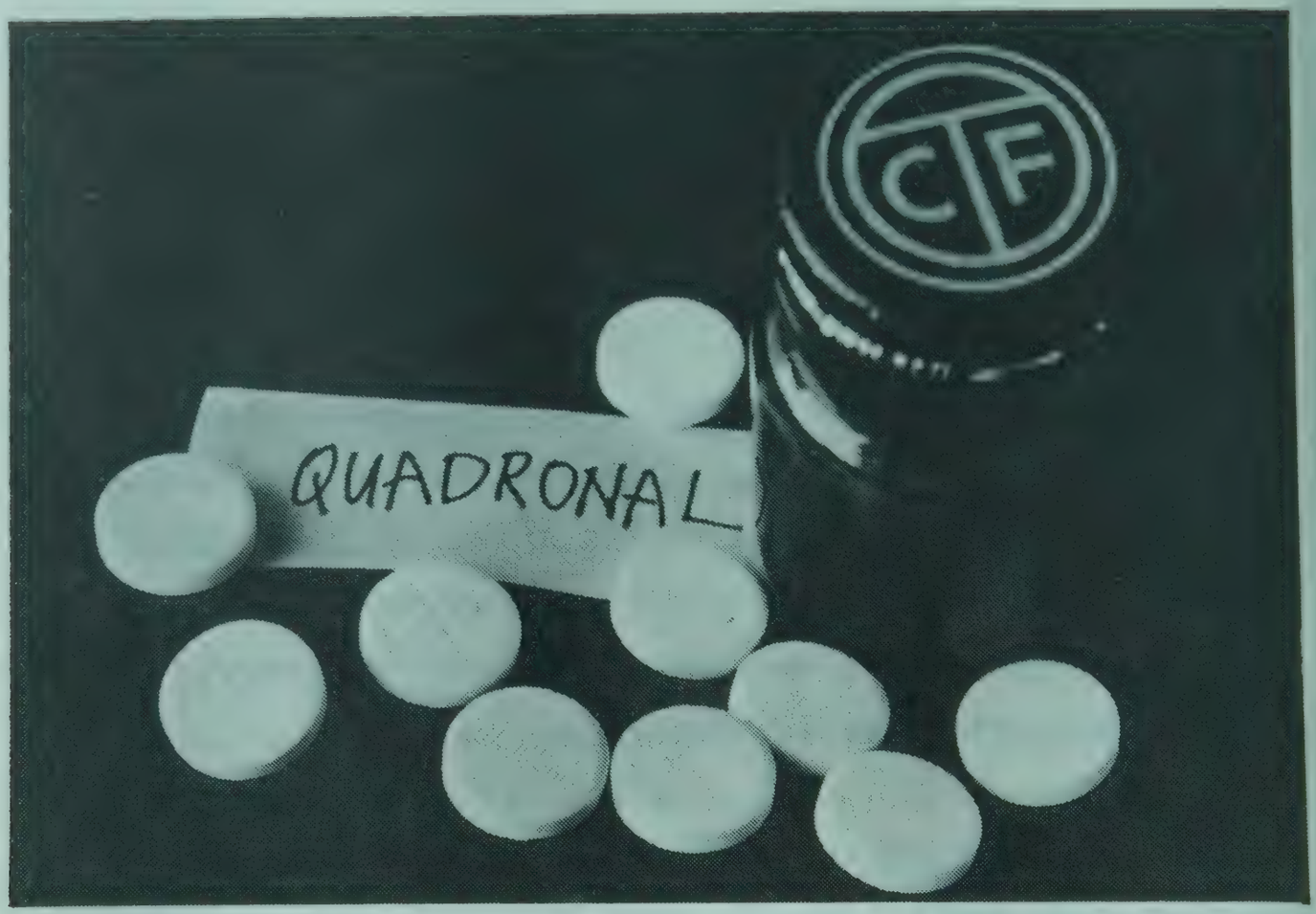

Quadronal tablets, which contain phenacetin. These tablets were purchased over the counter in Penang in early 1986.

	BRAND NAME	MANUFACTURER	CONTENTS	
			Codeine Phosphate	5 mg
			Hesperidin Methyl Chalcone	15 mg
			Vitamin C	70 mg
2.	QUADRONAL	Asta-Werke (Federal Republic of Germany)	Phenazone	150 mg
			Caffeine	50 mg
			Phenacetin	150 mg
			Lactylphenetidine	2.5 mg
3.	SOMA COMPOUND	Carter Wallace (United Kingdom)	Carisoprodol	200 mg
			Phenacetin	160 mg
			Caffeine	32 mg

(2) Warnings and Contraindications: Inadequate Information

Under the notes on 'Analgesics and Antipyretics' there is a section on 'Para-aminophenol Derivatives'. Information on these drugs is given in the following manner:

'Contra-Indications: Nephropathy

Special Precautions: Should be given with care to patients with impaired kidney or liver functions. Chronic use should be avoided. Daily use may potentiate oral anticoagulants.

It must be noted that there is hardly any information on phenacetin. No warnings are given on the dangers of this compound. Physicians are not warned that there should be monitoring of drugs containing this compound. Not enough stress is placed on restricting its use for the elderly. *DIMS* information on drugs containing this compound is not sufficient.

(3) Indications Given

Indications for the drugs listed include the following:

BENZA FORTE (Takeda)

'Indications: Common colds especially accompanied with cough and fever.

C/I: Pyrine hypersensitivity.'

QUADRONAL (Asta-Werke)

'Indications: All types of pain.

C/I & S/P: Acute intermittent porphyria, granulocytopenia, glucose-6-phosphate-dehydrogenase deficiency. Also see notes 4 section 4b.'

SOMA COMPOUND (Carter Wallace)

'Indications: Relief of pain and stiffness in those

traumatic, rheumatic and other conditions affecting muscles and joints; fever in rheumatic and other conditions.

C/I: Nephropathy

S/P: Reduce dose for the elderly. Impaired renal or hepatic function. Drowsiness may occur. Also see notes 4 section 4b.'

Besides the lack of information on adverse effects and contraindications, the information given in *DIMS* on the indications of the drugs is also insufficient.

The preparations listed 'Indications' for a wide range of ailments, including 'all types of pain', 'relief of pain and stiffness in those traumatic, rheumatic and other conditions affecting muscles and joints' and even for 'common colds especially accompanied with cough and fever'. If a drug containing a dangerous compound like phenacetin can be prescribed for 'all types of pain' then it is imperative that the authorities do something about restricting/banning its use immediately.

CHAPTER 5

DRUG INSERT FOR QUADRONAL

The drug insert for Quadronal in Malaysia was examined. It was found that the dangers of this drug were not sufficiently stressed (See Appendix).

Under 'Properties and indications' the following is said: 'Continuous headache can hamper very much daily work and efficiency. Migraine, toothache, neuralgic and rheumatic pain, fatigue due to extreme climatic changes, hangover due to abuse of alcohol and tobacco, common colds, discomfort during menstruation etc can reduce your general well-being considerably. Quadronal brings forth quick and reliable relief from pain and discomfort.' It is claimed that side effects 'have not been reported in appropriate therapy as directed'.

Under 'Administration and dosage' the following is recommended: 'Take one or several times daily 1-2 tablets or 1 suppository if not otherwise prescribed by the physician.' The dosage stated is very vague and this can easily give rise to overdosage.

There is no warning against kidney damage (papillary

necrosis) and liver damage which can occur when phenacetin is taken over a prolonged period in large doses. There is also no warning to say that when phenacetin is taken in doses of 1 gramme or more daily, blood disorders will occur.

Quadronal also contains an equal amount of phenazone (150mg). This drug has been shown to cause haemolytic anaemia in certain individuals with a deficiency of G6PD (*Martindale* 28th ed: 272). It is also liable to give rise to skin eruptions and in susceptible individuals even small doses may have this effect (Ibid).

It is frightening that Quadronal, which contains dangerous drugs like phenacetin and phenazone, is promoted by Asta-Werke for such trivial conditions as fatigue, hangover and 'discomfort during menstruation'.

CHAPTER 6

CASE REPORTS OF TOXICITY

Since local monitoring and surveillance of drugs containing phenacetin are inadequate, the full dangers of its adverse effects are not realised. However the following are two case reports of patients in other countries who suffered adverse reactions due to consumption of drugs containing phenacetin. One is a case of a man admitted to hospital with an acute bullous eruption while the other reports the case of a man found dead from a multiple drug reaction.

(1) First Case Report

An 84-year-old man was admitted to the Kyoto (Japan) University Hospital because of an acute bullous eruption. Seven days previously, he had been receiving oral medication for a common cold. His daily regimen included 900 mg of chlorpheniramine maleate, 600 mg of phenacetin, 400 mg of methylephedrine, 1500 mg of sulfapyridine and 300 mg of aminophylline.

The day prior to admission, the patient noted many non pruritic blisters. There was no history of long-term sun

exposure. The patient had a history of ischaemic heart disease of seven years' duration and had been treated with trimetazidine hydrochloride, dipyridamole, ubidecarenose, metildigoxine, etilefrine, hydrochloride and ajmaline. He also had had chronic whole-body eczema for the past three years; the skin lesions had been controlled well with a fluocinonide ointment.

Physical examination disclosed tense, non pruritic bullae of various sizes, measuring 1 to 10 cm in diameter, scattered mainly over the extremities. Some of the blisters were haemorrhagic. The blisters were easily ruptured, leaving severely painful erosions.

Since a drug-induced bullous disease was suspected, the medications for the upper respiratory tract infection were totally discontinued and the patient was treated with initial oral doses of betamethasone (3 mg daily) for two weeks. The bullous lesions cleared in one month, and the dosage of betamethasone was gradually reduced. Then, a single oral dose of phenacetin (60 mg) was given to the patient. Blisters returned within 12 hours. No blister followed administration of each of the other medications (noted previously) that the patient had taken for his cold. The recurrent eruption persisted, then gradually subsided, despite combined therapy with dapsone (100 mg daily) and betamethasone (1 to 2 mg daily) for three months. It can therefore be concluded that phenacetin was the causative factor in producing the bullous pemphigoid-like

lesions. (Kasihara 1984: 1196-1199).

(2) Second Case Report

A 35-year-old Caucasian male weighing 170 lbs was found dead on the kitchen floor of his residence in North Dakota, USA. The deceased was a known illicit drug user and had been taking aspirin alone or in combination with phenacetin and caffeine over a number of years for the relief of joint pains. Apart from a previous surgery for a duodenal ulcer, he had no other serious medical ailments. An autopsy of the victim revealed that he had been dead approximately one day. The heart blood and bladder urine were collected for toxicological analysis. The results showed the presence of propoxyphene, salicylate, caffeine and phenacetin. Acetaminophen also was present in the plasma in the urine.

When a single drug is involved the steady state tissue level of it is based on the quantity of ingestion and on the rates of absorption, metabolism, distribution and elimination. However, when other drugs are present not only are the rates of absorption, metabolism and distribution altered but it also results in a synergistic (cooperative interaction of different drugs) effect.

The level of propoxyphene (a non-narcotic analgesic which is prescribed for the relief of mild to moderate pain. It is often prescribed in combination with drugs such as aspirin, phenacetin, acetaminophen and caffeine) found

in the blood was in agreement with a value reported in a fatal poisoning and was considerably higher in the urine than that of the propoxyphene levels in fatalities. The amount of caffeine found in the study was several times less than the reported values of the drug in fatalities.

Very limited information is available on the human phenacetin levels in fatal poisonings. Wright et al (*Clinical Toxicology*, Vol 8, 1975: 457-463) have reported two phenacetin-associated deaths. In addition to phenacetin, one of the cases also involved codeine, aspirin and caffeine. The values of phenacetin, caffeine and salicylate concentrations in the case of the 35-year-old Caucasian male were several times higher than that of the values in the multi-drug fatality reported by Wright et al. The caffeine, acetaminophen and salicylate concentrations found in the present study were above the individual toxic level, and just below the fatal levels. Therefore it appears that the interaction between the drugs played a role in the rapid onset of the toxicity with a greater intensity leading to early death. (Chaturvedi, et al, 1983: 255-264).

CHAPTER 7

CONCLUSION

This report has attempted to make a case for the need to remove all phenacetin preparations from the market. In so doing, it has examined current studies on drugs containing phenacetin; legislation and action taken by health authorities on the drug worldwide; and information and marketing of this drug in Malaysia.

Phenacetin has been shown to be a drug with many side effects and which has no real advantage over other presently available preparations. There are on the market today alternative anti-inflammatory agents which are just as effective and without some of the lethal side effects associated with phenacetin. It would be worthwhile to quote once more the view of the British Committee on the Review of Medicines: 'Phenacetin has no place in analgesic, antipyretic and anti-inflammatory therapy.'

Drug companies cannot be allowed to promote such a toxic drug for minor ailments. This kind of promotion can lead to irrational drug prescription and drug use and to needless injury or death.

CAP strongly urges the Ministry of Health to recall all preparations containing this drug from the market immediately and ban the use of phenacetin in drugs for the safety and health of Malaysian consumers.

CAP would like to repeat its call for the setting up of an independent unit within the Ministry of Health to control and evaluate imported as well as locally manufactured drugs during all stages of manufacture, packing, storage, advertising and distribution of medicines. This body should comprise medical doctors, pharmacists and pharmacologists to look into all aspects and to advise legislation along the lines of the Food and Drug Administration (USA), the Committee on Safety of Medicines (UK) and the Expert Committee, Ministry of Health in Bangladesh. It is evident that multinational drug companies adopt lax standards in their marketing precisely because there are no mandatory requirements for them to do otherwise. Thus a 'watchdog' committee is urgently required to increase awareness and ensure corporate responsibility.

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APPENDIX

DRUG INSERT FOR QUADRONAL

Attention, read carefully!

Quadronal®

Brings forth rapid and reliable relief from pain.

Composition:	1 tablet	1 suppository
	contains mg.:	
Phenazone	150	300
Phenacetine	150	300
Lactylphenetidine	2.5	5
Caffeine	50	100

Properties and Indications: Continuous headache can hamper very much daily work and efficiency. Migraine toothache, neuralgic and rheumatic pain, fatigue due to extreme climatic changes, hangover due to abuse of alcohol and tobacco, common colds, discomfort during menstruation etc. can reduce your general well-being considerably.
Quadronal brings forth quick and reliable relief from pain and discomfort.

Administration and dosage: If not otherwise prescribed by the physician, take one or several times daily 1 - 2 tablets or 1 suppository. The tablets should be dissolved in water.

Side-effects: have not been reported in appropriate therapy as directed. Occasionally in very sensitive patients allergic skin reactions, in very rare cases granulocytopenia may occur. Pharyngitis may be the first symptom of a beginning granulocytopenia. In this case the patient should contact the physician.

Contraindications: Quadronal should not be used in case of: Acute intermittent porphyria, granulocytopenia, severe renal disorders, glucose-6-phosphate-dehydrogenase deficiency of genetic origin (symptom: haemolytic anaemia).

Attention: In case of persisting pain of unknown origin it is recommended to seek medical advice.
Children under 3 years of age should not take Quadronal.
Not to be administered to patients with kidney damage.

Presentation:
Tablets: Packs of 10, 20, 50, 250, 500 and 1.000
Suppositories: Packs of 5 and 50

Suppositories softened by heat should be immersed with the foil in cold water for a few minutes.

The list of presentation forms is not complete, and all mentioned packs are not available in all countries.

Store drugs carefully! Keep out of children's reach!

How to remove the suppository

ASTA-WERKE AG
Chem. Fabrik
D-4800 Bielefeld 14
Germany

Drugs and the Third World:

Phenacetin Risks, Benefits and Marketing in Malaysia

Phenacetin is a painkiller known to cause kidney damage and liver damage in large concentrations or over a long period of time. It is commonly used in combination with other painkilling drugs.

Many countries have either completely banned or severely restricted the use of phenacetin. In Malaysia it is listed as a Group B Poison, yet it is allowed to be used in combination products sold to the public.

This report reveals the toxicity and dangers of this drug and calls for a total ban on its use in Malaysia.

In October 1986, a few months after CAP sent this report to the Malaysian Ministry of Health, the government banned the sale of phenacetin in Malaysia.

The Consumers' Association of Penang (CAP) is a non-profit making organisation which fights for the rights and interests of Malaysian consumers through research, educational and representational activities.

The issues it takes up include the fulfilment of basic needs (food, nutrition, health, housing, transport, etc.), food and product safety, environmental pollution and problems, the rational use of resources, specific problems of women, and business malpractices.

This is part of a series of CAP Reports aimed at providing the public with the results of some of the important areas of CAP's activities. It is hoped that this series will generate public interest and awareness, and help to contribute towards a better life for Malaysians.

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ISBN: 967 – 9950 – 25 – 5